Comparison of Ultrasound Elastography and Color Doppler Ultrasonography for Distinguishing Small Triple-Negative Breast Cancer From Fibroadenoma

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Objectives—To compare the performance of ultrasound elastography and color Doppler ultrasonography (US) in distinguishing small, oval, or round triple-negative breast cancer from fibroadenoma and the influence on the further management decision at US.

Methods—In total, 131 biopsy-proven oval or round fibroadenomas (n = 68) and triple-negative breast cancers (n = 63) smaller than 2 cm were included. Three blinded readers assessed the images from US, elastography, and color Doppler imaging according to the Breast Imaging Reporting and Data System lexicon independently. Interobserver agreement was assessed, and sensitivity, specificity, accuracy, and area under the receiver operating characteristic curve values for each data set were compared. Pathologic results were reference standards.

Results—The interobserver agreements were excellent (intraclass correlation coefficients, 0.856 for US, 0.948 for elastography, and 0.864 for color Doppler). The specificity and accuracy of US with elastography were increased compared with US alone or US with Doppler imaging without statistically significant differences in sensitivity. The average area under the curve for US with elastography (0.869) was increased compared with US alone (0.650) or US with color Doppler (0.576).

Conclusions—Elastography is more useful than color Doppler imaging for distinguishing small, oval, or round triple-negative breast cancer from fibroadenoma, and elastography can help avoid biopsy of benign masses.

Key Words—breast; color Doppler ultrasonography; elastography; fibroadenoma; triple-negative breast cancer; ultrasonography

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Abbreviations

A_z, area under the curve; BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; ICC, intraclass correlation coefficient; ROC, receiver operating characteristic; US, ultrasonography

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Triple-negative breast cancer is a distinctive subgroup of breast cancer that does not express estrogen receptors, progesterone receptors, or human epidermal growth factor receptor 2. Triple-negative breast cancer is associated with a relatively young age, aggressive histologic and clinical behavior, and a poor prognosis.[1–4]

There is an increasing emphasis on defining the imaging characteristics according to breast cancer subtypes, and triple-negative breast cancer has been studied widely regarding its imaging features on mammography, ultrasonography (US), and magnetic resonance imaging. Several retrospective studies related to the conventional US characteristics of triple-negative breast cancer suggested that it was more likely to show benignlike features, such as an oval or round shape and a smooth and circumscribed margin, and was less likely to show an echogenic halo compared with non–triple-negative breast cancer.[5–8] In this regard, there may be false-negative results in the evaluation of triple-negative breast cancer, which would lead to a delayed diagnosis and a potentially worse clinical outcome for the patient.[3–6] Furthermore, a recent study about the tumor volume doubling time revealed that triple-negative breast cancer has the fastest growth among the 3 subtypes of breast cancer.[9]

Recent studies have investigated the use and efficacy of ultrasound elastography and color Doppler US for further characterization of breast lesions. Several clinical studies and retrospective analyses have reported that the combined use of elastography or color Doppler imaging with US is useful for the differentiation of benign from malignant breast lesions, with increasing sensitivity and specificity.[10–12] In addition, Cho et al[11] suggested that the combined use of both elastography and color Doppler imaging with US could increase the diagnostic accuracy in distinguishing benign breast lesions from malignancies and the specificity in decision-making for biopsy recommendation at US. However, to our knowledge, there have been no studies about the added value of elastography and color Doppler imaging with US in distinguishing small, oval, or round triple-negative breast cancer from fibroadenoma. Therefore, the purpose of this study was to retrospectively compare the diagnostic performance of elastography and color Doppler imaging for distinguishing small, oval, or round triple-negative breast cancer from fibroadenoma and its influence on further management on the basis of US.

Materials and Methods

Patients and Lesions

This retrospective study was approved by the Institutional Review Board, and informed consent was not required. Between January 2012 and September 2015, 342 consecutive women who were confirmed to have triple-negative breast cancer were identified from the electronic medical database of our institution. In total, 257 patients were excluded from this study for the following reasons: 91 patients had no available US images, such as 2 orthogonal images, elastography, or color Doppler; 77 patients received neoadjuvant chemotherapy; 49 patients had larger than 2-cm breast cancer; 29 patients had diffuse or nonmass breast cancer; and 11 patients underwent excision of breast cancer before visiting our institution. Ninety triple-negative breast cancer lesions in 85 patients were enrolled in this analysis initially. Among the 90 triple-negative breast cancer lesions, 27 irregularly shaped lesions that were assessed by all of 3 readers were excluded because of their irregular shape. Finally, 63 triple-negative breast cancer lesions in 59 patients were included in this study. In the same period, 68 biopsy-confirmed oval or round fibroadenomas in 66 patients were also enrolled as a control group. We sorted patients with fibroadenoma randomly by matching the size of the lesion with triple-negative breast cancer from the biopsy-pathologic database in our department. Finally, a total of 131 breast lesions in 125 patients that were oval or round and smaller than 2 cm and the respective US, elastographic, and color Doppler images were included in this study. Fifty-five percent (35 of 63) of triple-negative breast cancer and 32% (22 of 68) of fibroadenoma cases were palpable.

The pathologic results of the lesions were reference standards. triple-negative breast cancer included infiltrating ductal carcinoma ($n = 59$), invasive lobular carcinoma ($n = 1$), invasive papillary carcinoma ($n = 1$), secretory carcinoma ($n = 1$), and metaplastic carcinoma ($n = 1$). The biopsies were performed by 1 of 6 radiologists who had 2 to 7 years of experience in breast US and interventions in our institution.

Ultrasonographic examinations including B-mode US, elastography and color Doppler US

Ultrasonographic examinations were performed with a 6–14-MHz linear transducer on an EUB-8500 US system (Hitachi Medical, Tokyo, Japan) or a 4–15-MHZ linear transducer on an Aixplorer US system (SuperSonic Imagine SA, Aix-en-Provence, France) by 1 of 9 radiologists with 1 to 15 years of experience in performing and interpreting breast US. All radiologists had at least 10 months of experience (at least 300 cases) in data acquisition and interpretation of elastographic and color Doppler images before this study.

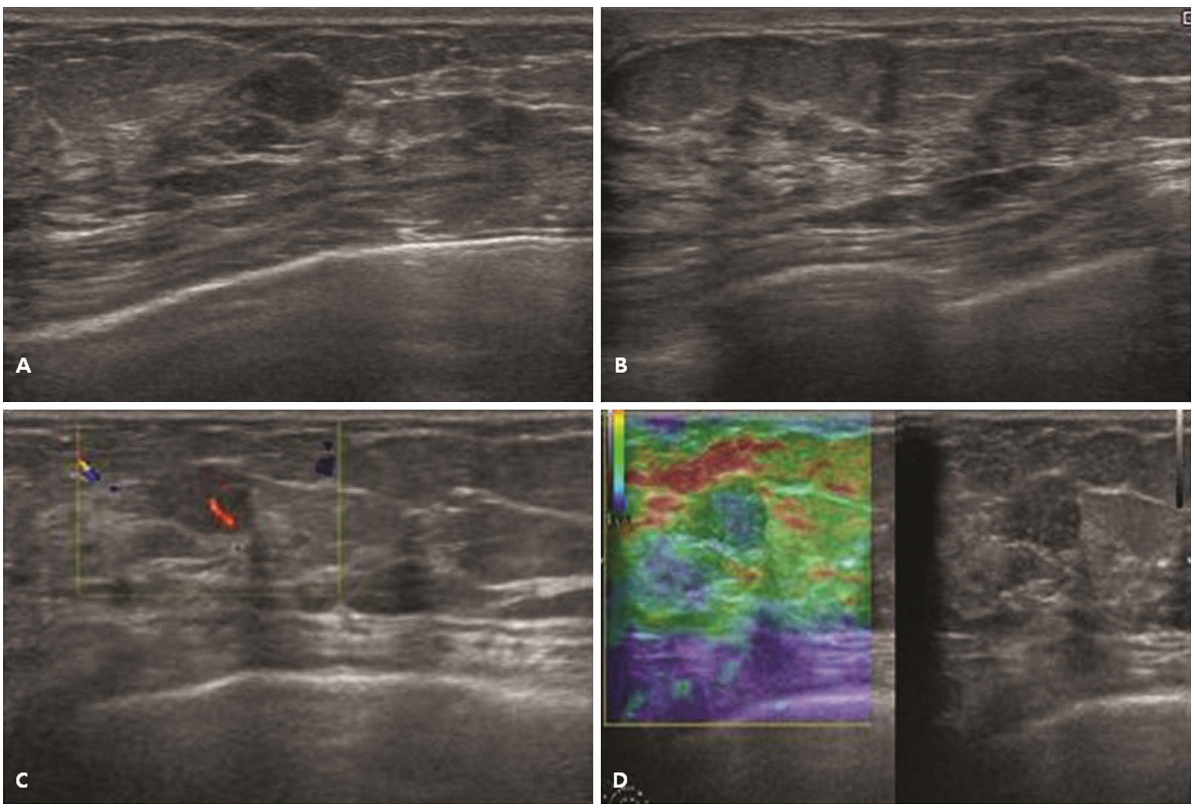
Images from US were displayed in 2 orthogonal views, such as transverse and longitudinal scans or radial and anteradial scans. After identification of a lesion on US, elastographic and color Doppler images were saved separately. The elastographic and color Doppler images consisted of split-screen images of B-mode US and elastography or color Doppler imaging. For elastography, a measurement box was adjusted to focus on the target lesion and to include a sufficient amount of adjacent normal breast tissue and the surrounding subcutaneous fat layer and the superficial portion of the pectoralis muscle layer. The transducer was placed over the target lesion vertically with light repetitive compression by the transducer during a strain elastographic examination. In the case of shear wave elastography, compression or movement of the transducer was minimized by using a generous amount of contact jelly to reduce artifacts and obtain adequate data.[13] For the color Doppler examination, the color box was adjusted to the focus of the target lesion with a minimal amount of normal surrounding tissue. Minimal pressure was applied with the transducer to prevent obliteration of small vessels in the lesion. The color gain was set to a level that could identify low velocity flow in the lesion and minimize background noise, ranging from ± 6.0 to ± 4.0 cm/s.

It took 4 to 5 minutes to evaluate US, including US, elastography, and color Doppler images, by 1 of 9 experienced radiologists. Fifty of 131 lesions were biopsied before US evaluations in our institution. The other lesions were pathologically confirmed by image-guided core needle biopsy in our institution after the US evaluation.

Readers and Reading Procedures

Three radiologists with 4 to 25 years of experience in breast US who had not performed the US examinations participated as readers. All readers were blinded to mammographic, clinical, and histologic findings and the proportion of cases with fibroadenoma and triple-negative breast cancer. Reading of 2 orthogonal US images only was performed initially. Readers assessed the margin, orientation, internal echogenicity pattern, and posterior acoustic features of the lesion on US according to the Breast Imaging Reporting and Data System (BI-RADS) lexicon and scored the likelihood of malignancy by BI-RADS criteria considering subcategorization of BI-RADS category 4 into 4a, 4b, and 4c.[14] They assessed the likelihood of malignancy with BI-RADS categorization from 3

Figure 1. Images from a 38-year-old woman with fibroadenoma. **A** and **B**, B-mode images of orthogonal views showing an oval hypoechoic mass. **C**, Color Doppler image showing intralesional vascularity, suggesting a Doppler score of 3. **D**, Elastographic image showing almost entire the lesion as green on strain elastography, suggesting an elasticity score of 1.



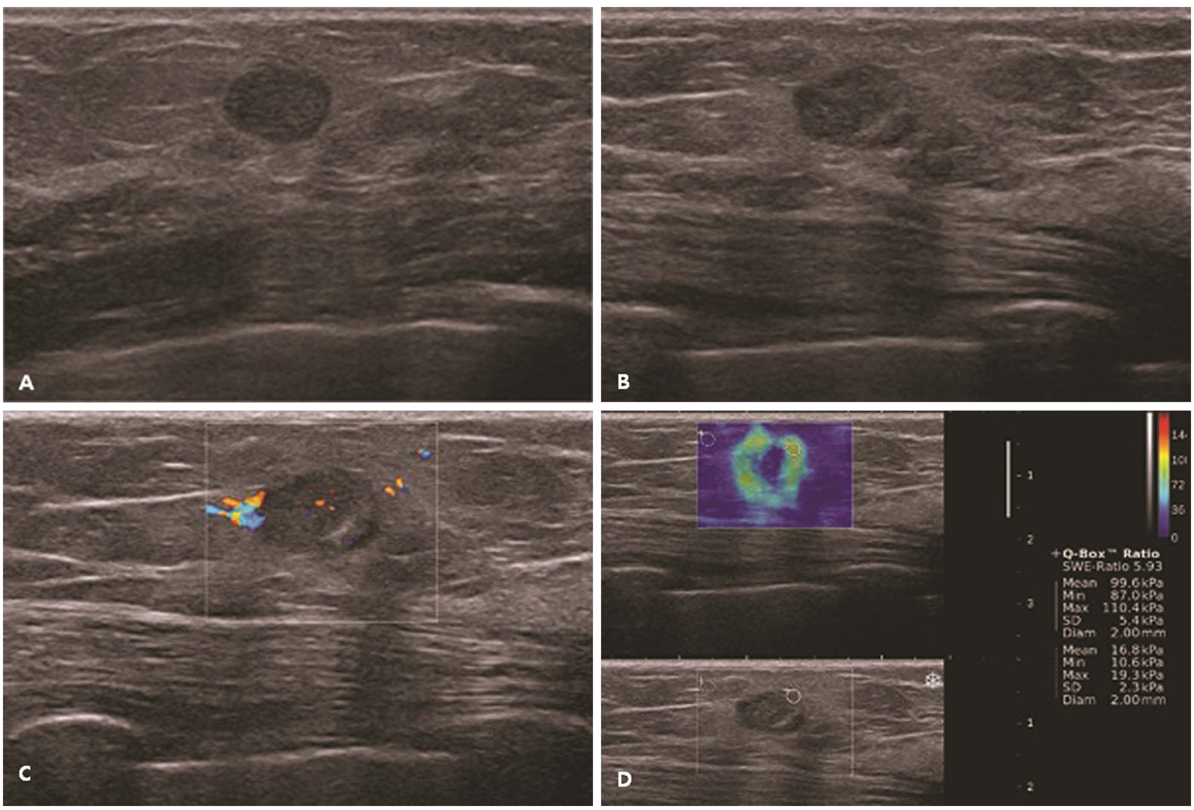
to 5 in 5 scales (3, 4a, 4b, 4c, and 5). Category 3 indicated a likelihood of malignancy of less than 2%, and the lesion does not need a biopsy. In a lesion of with category 4a or higher, the likelihood of malignancy increases from 3% to 100%, and the lesion needs a biopsy. After assessment of US images, elastographic and color Doppler images were evaluated.

The color Doppler score was categorized as 1, 2, or 3 according to the BI-RADS lexicon (Figures 1–3).[14] A score of 1 was given when no vascularity was observed in or around the mass. A score of 2 was given when vascularity was observed at the rim of the mass. A score of 3 was given when internal vascularity was observed in the mass.

The elastographic score was categorized into 3 divisions that were soft scored as 1, intermediate scored as 2, and hard scored as 3 according to the BI-RADS lexicon.[14] On strain elastography, a score of 1 was given when the elasticity showed even strain across the entire lesion or a mosaic pattern of green and blue (Figure 1), as for Tsukuba score 1 or 2 by Itoh et al.[15] A score of 2 was given when the elasticity showed central blue and peripheral green, as for Tsukuba score 3. A score of 3 was given when the entire lesion, surrounding lesion, or both were blue, as for Tsukuba score 4 or 5. On shear wave elastography, the elasticity could be shown as colors or an elasticity value (kilopascals), which could be classified into 3 categories: dark blue and light blue (soft, ≤ 72 kPa) as negative and scored as 1, green and orange (intermediate, 72–108 kPa) as equivocal and scored as 2, and red (hard, ≥ 108 kPa) as positive and scored as 3 (Figure 2).[13]

The readers were asked to change their initial US assessment by combining elastographic and color Doppler scores. For combined assessment of US and either elastography or color Doppler imaging, the BI-RADS category was upgraded 1 category strictly for hard or hypervascular masses, not changed for intermediate or

Figure 2. Images from a 57-year-old woman with triple-negative breast cancer. **A** and **B**, B-mode images of orthogonal views showing an oval hypoechoic mass. **C**, Color Doppler image showing peripheral and intralesional vascularity, suggesting a Doppler score of 3. **D**, Elastographic image showing orange to red areas with maximal elasticity of 110 kPa on shear wave elastography, suggesting an elasticity score of 3.



hypovascular masses, and downgraded 1 category for soft or avascular masses. In addition, the readers reassessed the likelihood of malignancy of lesions under the consideration of both elastographic and color Doppler scoring. Positivity was considered BI-RADS category 4a or higher, with a decision to perform biopsy. Negativity was considered BI-RADS category 3 or lower, with a decision not to perform biopsy

Data and Statistical Analysis

Interobserver agreement among the 3 readers regarding the scores of the likelihood of malignancy on US alone, elasticity scores of the lesions, and color Doppler scores of the lesions was evaluated by using intraclass correlation coefficients (ICCs), which were defined as follows: an ICC of 0 to 0.20 indicated no agreement; 0.21 to 0.40, poor agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, good agreement; and than 0.80, excellent agreement. The sensitivity, specificity, and accuracy of US alone were compared with the other 3 data sets (US with elastography, US with color Doppler, and US with both elastography and color Doppler) by the McNemar test.

To evaluate the radiologists' performance of the 4 US data sets for distinguishing triple-negative breast cancer from fibroadenoma, a receiver operating characteristic (ROC) curve analysis was performed. $P < .05$ was considered to indicate a significant difference. Negative likelihood ratios, defined as (1 – sensitivity)/specificity, were also calculated for US alone, US with elastography, US with color Doppler, and US with both elastography and color Doppler. A negative likelihood ratio of less than 0.1 was considered excellent diagnostic value; 0.1 to 0.2, good diagnostic value; 0.2 to 1, poor diagnostic value; and 1, no diagnostic value.[16]

Management decision changes from either follow-up to biopsy or biopsy to follow-up were also evaluated for fibroadenoma and triple-negative breast cancer. To

Figure 3. Images from a 66-year-old woman with triple-negative breast cancer. **A** and **B**, B-mode US images of orthogonal views showing an oval hypoechoic mass. **C**, Color Doppler image showing the mass without vascularity, suggesting a Doppler score of 1. **D**, Elastographic image showing a blue area with maximal elasticity of 20 kPa on shear wave elastography, suggesting an elasticity score of 1.

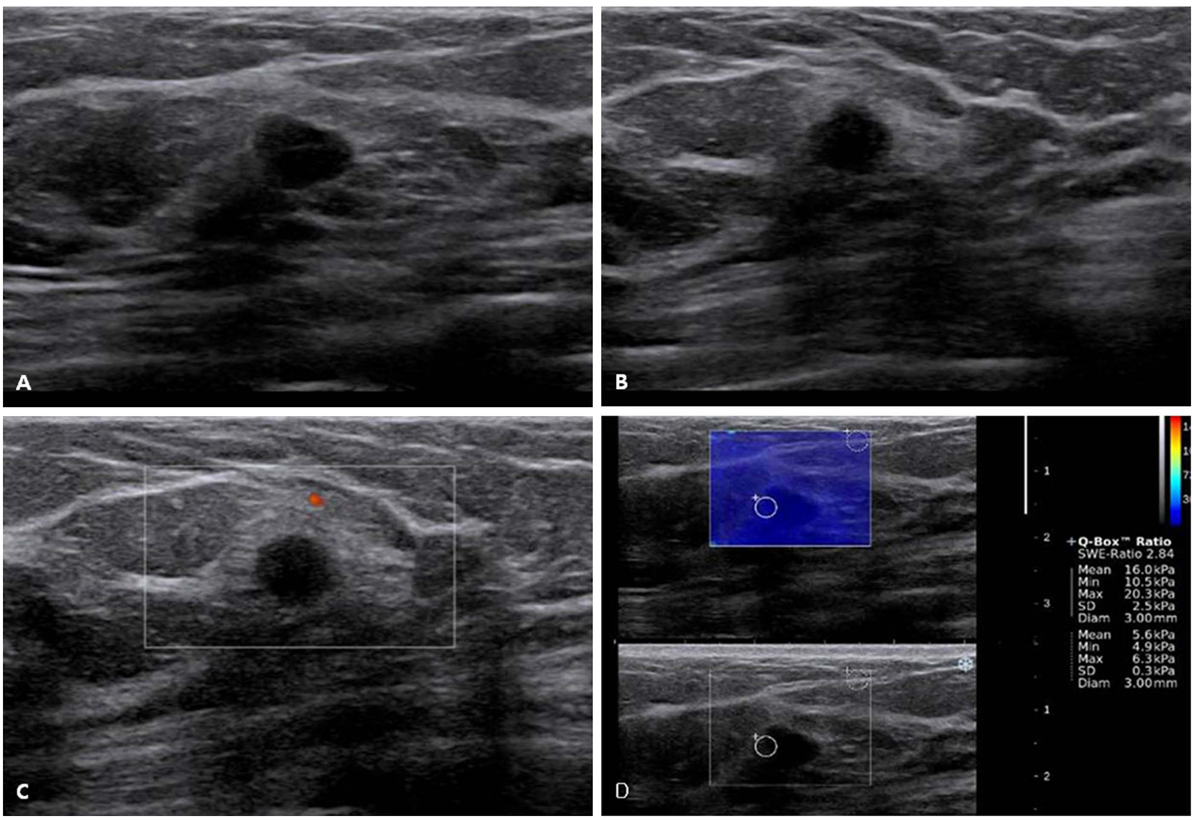


Table 1. Clinicopathologic Characteristics

Parameter	Fibroadenoma (n = 68)	Triple-Negative Breast Cancer (n = 63)	*P*
Age, y	43.74 (27–70)	50.48 (30–77)	<.001
≤50	54	27	
>50	14	36	
Size, mm	13.3 (6–20)	13.3 (6–20)	.991
≤10	22	21	
10–20	46	42	
Symptom			.241
Asymptomatic	42	27	
Palpable	22	35	
Pain	4	1	

Data are presented as mean (range) where applicable.

further evaluate the ability of elastography or color Doppler US ability to downgrade and potentially obviate negative biopsy results, we excluded the cases showing noncircumscribed or nonparallel findings, which would require biopsy regardless of elastographic or color Doppler findings, on US and reanalyzed the results with only BI-RADS category 3, 4a, and 4b lesions.

All statistical analyses except the ROC analysis were performed with commercially available software (SPSS statistics version 23.0 for Windows; IBM Corporation, Armonk, NY). The ROC analysis was performed with MedCalc version 13.0 for Windows; MedCalc, Mariakerke, Belgium).

Results

Patient Characteristics

The clinicopathologic characteristics of the patients are shown in Table 1.

Reader Agreement

The 3 readers had excellent agreement, with an ICC of 0.856 (95% confidence interval [CI], 0.808–0.894) for BI-RADS category assessment with US alone. The ICCs for the elastographic score assessment, color Doppler score assessment, BI-RADS category assessment combined with either elastography or color Doppler, and BI-RADS category assessment combined with both elastography and color Doppler were 0.948 (95% CI, 0.930–0.962), 0.864 (95% CI, 0.818–0.900), 0.942 (95% CI, 0.922–0.957), 0.837 (95% CI, 0.782–0.880), and 0.934 (95% CI, 0.912–0.952), respectively.

B-Mode US Features of Fibroadenoma and Triple-Negative Breast Cancer

The US features of fibroadenoma and triple-negative breast cancer for each reader are listed in Table 2. Among them, the margin and orientation of triple-negative breast cancer were significantly different from those of fibroadenoma for all 3 readers. The BI-RADS category assessments of the lesions were also significantly different between fibroadenoma and triple-negative breast cancer for all 3 readers.

We also evaluated the ICC value of each parameter. The 3 readers showed excellent agreement in the orientation of the lesion only, with an ICC of 0.823 (95% CI, 0.763–0.870). The ICC for assessing the margin showed good agreement, at 0.661. The ICC values for the echo pattern and posterior acoustic features showed moderate agreement, at 0.477 and 0.574, respectively.

Sensitivity, Specificity, Accuracy, and ROC Analysis

The sensitivity and specificity of each data set for each reader to distinguish triple-negative breast cancer from fibroadenoma based on the binary management recommendation of whether to perform biopsy are listed in Table 3. The specificity of US increased dramatically by adding elastography or both elastography and color Doppler on the basis of US, with statistically significant differences for all 3 readers. The sensitivity of US slightly decreased by adding elastography or color Doppler, but statistically significant differences were not observed. When color Doppler was added to US alone, the sensitivity, specificity, and accuracy were reduced compared with US alone for all 3 readers without statistically significant differences.

The ROC analysis showed that the area under the curve (A_z) of US with elastography (0.869 ± 0.036) was increased compared with US with color Doppler (0.576 ± 0.543) and highest among all data sets. In addition, the A_z of breast US was reduced when color Doppler was combined with US for all 3 readers. The A_z of US with both elastography and color Doppler (0.774 ± 0.072) was increased compared with US alone (0.650 ± 0.059) for all 3 readers (Table 3).

Negative Likelihood Ratio

The negative likelihood ratios of US with elastography and US with both elastography and color Doppler were lower than 0.1, meaning excellent diagnostic value for all 3 readers (Table 4). Also, the negative likelihood ratios of US with both elastography and color Doppler showed excellent results versus US with elastography, although the accuracy of US with both elastography and color Doppler was lower than that of US with elastography.

Management Decision Change

With regard to the management decision (either biopsy or follow-up), biopsy decisions were correctly changed to follow-up for a mean of 18.3 cases (26.9%; range, 15–21), and follow-up decisions were incorrectly changed to biopsy for a mean of 1.0 cases (1.4%; range 0–2) in the fibroadenoma group. In comparison, follow-up decisions were correctly changed to biopsy for a mean of 2.3 cases (3.6%; range 2–3), and biopsy decisions were incorrectly changed to follow-up for a mean of 2.0 cases (3.1%; range 1–4) in the triple-negative breast cancer group (Table 5).

Subgroup Analysis of BI-RADS Category 3, 4a, and 4b Lesions

In the subgroup analysis, the lesions with a noncircumscribed margin or nonparallel orientation masses assessed by all 3 readers were excluded, and the remaining lesions correspond to the BI-RADS categories 3, 4a, and 4b. A total of 73 lesions (54 fibroadenomas and 19 triple-negative breast cancers) assessed as BI-RADS category 3, 4a, and 4b lesions were included in subgroup analysis. The sensitivity, specificity, diagnostic accuracy, and ROC analysis for category 3, 4a, and 4b lesions

Table 2. B-Mode US Features of Fibroadenoma and Triple-Negative Breast Cancer by 3 Readers

US Feature	Fibroadenoma					Triple-Negative Breast Cancer					
Margin	Circumscribed	Noncircumscribed				Circumscribed	Noncircumscribed				P[a]
Reader 1	32	36 (13/11/12/0)				14	49 (11/23/10 /5)				.002
Reader 2	41	27 (23/0/4/0)				11	52 (35/5/10/2)				.001
Reader 3	36	32 (2/0/30/0)				3	60 (9/10/33/8)				.001
Echo pattern	**Hypo**	**Iso**	**Complex**	**Hetero**		**Hypo**	**Iso**	**Complex**	**Hetero**		
Reader 1	47	17	0	4		45	1	2	15		.417
Reader 2	47	19	1	1		52	6	1	4		.361
Reader 3	38	26	1	3		46	6	3	8		.199
Orientation	**Parallel**	**Non-parallel**				**Parallel**	**Non-parallel**				
Reader 1	59	9				30	33				.001
Reader 2	62	6				43	20				.001
Reader 3	60	8				41	22				.001
Posterior acoustic features	**None**	**Enhanced**	**Shadow**	**Combined**		**None**	**Enhanced**	**Shadow**	**Combined**		
Reader 1	34	24	2	8		26	26	1	10		.379
Reader 2	39	27	2	0		26	35	2	0		.095
Reader 3	53	8	2	5		25	19	3	16		.001
BI-RADS category	**3**	**4a**	**4b**	**4c**	**5**	**3**	**4a**	**4b**	**4c**	**5**	
Reader 1	23	43	2	0	0	3	28	21	10	1	<.001
Reader 2	15	51	2	0	0	2	30	27	4	0	<.001
Reader 3	32	34	2	0	0	3	19	21	9	11	<.001
Elasticity score	**1**	**2**	**3**			**1**	**2**	**3**			
Reader 1	60	6	2			8	10	45			.001
Reader 2	51	13	4			8	12	43			.001
Reader 3	55	8	5			11	9	43			.001
Doppler score	**1**	**2**	**3**			**1**	**2**	**3**			
Reader 1	30	14	24			15	20	28			.029
Reader 2	10	36	22			7	12	44			.001
Reader 3	29	25	14			15	25	23			.016

Data in parenthesis are the numbers of indistinct/angular/microlobulated/spiculated masses.
[a]Student t test.

showed similar trends compared with all cases (Table 3). In the negative likelihood ratio analysis, US with elastography and US with both elastography and color Doppler were lower than 0.1, meaning excellent diagnostic value by at least 1 reader (Table 4). For management decision changes, the trends were similar between all cases and the subgroup analysis and only one 0.8-cm oval triple-negative breast cancer was misclassified as benign by all 3 readers in the subgroup analysis (Table 5 and Figure 3).

Discussion

Our results suggest that the use of combined elastography with US is effective for radiologists in distinguishing small, oval, or round triple-negative breast cancer from

Table 3. Sensitivity, Specificity, Accuracy, and ROC analysis in Distinguishing Triple-Negative Breast Cancer From Fibroadenoma by 3 Readers

Parameter	US Alone	US + Elastography	P^a	US + Doppler	P^b	US + Elastography and Doppler	P^c
All Cases							
Sensitivity, %[d]	95.77 ± 0.92	91.53 ± 2.42		88.36 ± 2.42		96.27 ± 2.39	
Reader 1	95.24 (60/63)	92.06 (58/63)	.289	88.89 (56/63)	.227	96.83 (61/63)	>.999
Reader 2	96.83 (61/63)	88.89 (56/63)	.07	90.48 (57/63)	.125	98.41 (62/63)	>.999
Reader 3	95.24 (60/63)	93.65 (59/63)	.508	85.71 (54/63)	.146	93.65 (59/63)	>.999
Specificity, %[e]	34.31 ± 12.5	82.36 ± 5.30		26.96 ± 13.34		67.15 ± 17.42	
Reader 1	33.82 (23/68)	86.76 (59/68)	<.001	25.00 (17/68)	.311	76.47 (52/68)	<.001
Reader 2	22.06 (15/68)	76.47 (52/68)	<.001	14.71 (10/68)	>.999	47.06 (32/68)	<.001
Reader 3	47.06 (32/68)	83.82 (57/68)	<.001	41.18 (28/68)	>.999	77.94 (53/68)	<.001
Accuracy, %	63.87 ± 6.12	86.77 ± 3.77		56.49 ± 5.76		81.17 ± 8.16	
Reader 1	63.36 (83/131)	89.31 (117/131)		55.73 (73/131)		86.26 (113/131)	
Reader 2	58.02 (76/131)	82.44 (108/131)		51.15 (67/131)		71.76 (94/131)	
Reader 3	70.23 (92/131)	88.55 (116/131)		62.60 (82/131)		85.50 (112/131)	
A_z	0.650 ± 0.059	0.869 ± 0.036		0.576 ± 0.543		0.774 ± 0.072	
Reader 1	0.645 (0.557–0.727)	0.894 (0.828– 0.941)	<.001	0.569 (0.480–0.656)	.038	0.739 (0.655–0.811)	.009
Reader 2	0.594 (0.505–0.679)	0.827 (0.751– 0.887)	<.001	0.526 (0.437–0.614)	.087	0.727 (0.643–0.801)	<.001
Reader 3	0.711 (0.626–0.787)	0.887 (0.820–0.936)	<.001	0.634 (0.546–0.717)	.121	0.858 (0.786–0.913)	<.001
Subgroup analysis							
Sensitivity, %	87.72 ± 3.04	91.23 ± 6.08		85.96 ± 3.04		92.98 ± 3.05	
Reader 1	89.47 (17/19)	94.74 (18/19)	>.999	89.47 (17/19)	>.999	89.47 (17/19)	>.999
Reader 2	89.47 (17/19)	84.21 (16/19)	>.999	84.21 (16/19)	>.999	94.74 (18/19)	>.999
Reader 3	84.21 (16/19)	94.74 (18/19)	.625	84.21 (16/19)	>.999	94.74 (18/19)	.625
Specificity, %	43.21 ± 15.75	77.78 ± 10.31		37.03 ± 8.07		67.90 ± 16.70	
Reader 1	42.59 (23/54)	66.67 (36/54)	<.001	40.74 (22/54)	>.999	66.67 (36/54)	<.001
Reader 2	27.78 (15/54)	79.63 (43/54)	<.001	27.78 (15/54)	.115	51.85 (28/54)	.002
Reader 3	59.26 (32/54)	87.04 (47/54)	<.001	42.59 (23/54)	.122	85.19 (46/54)	<.001
Accuracy, %	54.79 ± 10.95	81.28 ± 7.54		49.77 ± 6.32		74.43 ± 12.43	
Reader 1	54.79 (40/73)	73.97 (54/73)		53.42 (39/73)		72.60 (53/73)	
Reader 2	43.84 (32/73)	80.82 (59/73)		42.47 (31/73)		63.01 (46/73)	
Reader 3	65.75 (48/73)	89.04 (65/73)		53.42 (39/73)		87.67 (64/73)	
A_z	0.727 ± 0.048	0.867 ± 0.096		0.710 ± 0.066		0.893 ± 0.059	
Reader 1	0.745 (0.629–0.840)	0.954 (0.877–0.989)	.002	0.712 (0.595–0.812)	.679	0.826 (0.719–0.905)	.207
Reader 2	0.673 (0.553–0.778)	0.883 (0.786–0.946)	.001	0.643 (0.523–0.752)	.531	0.911 (0.821–0.965)	.001
Reader 3	0.764 (0.687–0.882)	0.944 (0.864–0.984)	.005	0.775 (0.662–0.864)	.709	0.941 (0.860–0.983)	.011

Data are presented as mean ± SD where applicable. Values in parentheses are numbers and 95% CIs where applicable. Subgroup analysis includes the lesions assessed as BI-RADS categories 3, 4a, and 4b by all 3 readers.
[a]Comparison between B-mode US alone and B-mode US with elastography.
[b]Comparison between B-mode US alone and B-mode US with Doppler.
[c]Comparison between B-mode US alone, B-mode US with elastography, and B-mode US with Doppler.
[d]Biopsy recommendation rate for triple-negative breast cancer.
[e]Follow-up recommendation rate for fibroadenoma.

fibroadenoma compared with US alone. In addition, we found that US with both elastography and color Doppler imaging can yield better results for radiologists in diagnostic performance than US alone, as previous studies regarding the differentiation between benign and malignant breast lesions using elastography or color Doppler imaging have demonstrated.[11,12,17–20] However, the addition of color Doppler imaging alone can yield worse results in diagnostic accuracy than US alone. The ROC analysis showed that the A_z of US with elastography was highest among the 4 data sets, and the A_z of breast US was decreased when color Doppler imaging was combined with B-mode US for all 3 readers. Similar trends were found when only BI-RADS category 3, 4a, and 4b lesions were included in the analysis. There have been few reports regarding the efficacy of elastography in small breast lesions (<2 cm), and these studies suggested that elastography was helpful in the diagnosis of small breast cancer and differentiation of benign breast lesions from malignant lesions.[19,21] To the best of our knowledge, this work was the first study regarding the diagnostic efficacy of elastography and color Doppler US for differentiation of small, oval, or round shape triple-negative breast cancer from fibroadenoma.

In this study, we limited the mass size to less than 2 cm because as the mass size grew, the differentiation between benign and malignant lesions could be easily determined, and the role of elastography or color Doppler could be less important. In addition, we confined the shape of the mass to only oval or round because in the case of an irregularly shaped lesion, biopsy would have been performed on the basis of the morphologic criteria regardless of the elastographic or color Doppler results. In our study, the prevalence (63/90) of oval or round masses in triple-negative breast cancer was higher than in other reports[5,8] since irregularly shaped masses were excluded only when all 3 readers read the shape as irregular.

The elasticity of breast masses is harder in malignant lesions than in benign lesions and harder in infiltrative breast malignancy than in in situ lesions, indicating that the negative predictive value of a negative elasticity score is 99.3%.[15,19,22–24] Berg et al[24] suggested that the maximum lesion diameter had a significant impact on

Table 4. Negative Likelihood Ratios in 4 Diagnostic Sets by 3 Readers

Analysis	US Alone	US + Elastography	US + Doppler	US + Elastography and Doppler
All cases				
Reader 1	0.1407	0.0915	0.4444	0.0539
Reader 2	0.1436	0.1038	0.6472	0.0338
Reader 3	0.1011	0.0758	0.3470	0.0814
Mean ± SD	0.1284 ± 0.0237	0.0903 ± 0.0140	0.4795 ± 0.1531	0.0563 ± 0.0238
Subgroup analysis				
Reader 1	0.2472	0.0789	0.2584	0.1579
Reader 2	0.379	0.1666	0.5683	0.1014
Reader 3	0.2664	0.0604	0.3707	0.0617
Mean ± SD	0.2975 ± 0.0712	0.1019 ± 0.0567	0.3991 ± 0.1568	0.1070 ± 0.0483

Table 5. Changes in Biopsy Recommendation for US With Elastography and Color Doppler Imaging

Analysis	Follow-up to Biopsy	Biopsy to Follow-up	Follow-up to Biopsy	Biopsy to Follow-up
All cases	Fibroadenoma (n = 68)		Triple-negative breast cancer (n = 63)	
Reader 1	1 (1/23)	15 (15/45)	2 (2/3)	1 (1/60)
Reader 2	2 (2/15)	19 (19/53)	2 (2/2)	1 (1/61)
Reader 3	0 (0/32)	21 (21/36)	3 (3/3)	4 (4/60)
Mean ± SD	1.0 ± 0.89	18.3 ± 3.05	2.3 ± 0.57	2.0 ± 1.7
Subgroup analysis	Fibroadenoma (n = 54)		Triple-negative breast cancer (n = 19)	
Reader 1	1 (1/22)	23 (23/32)	2 (2/2)	1 (1/17)
Reader 2	2 (2/15)	15 (15/39)	2 (2/2)	1 (1/17)
Reader 3	0 (0/32)	14 (14/22)	3 (3/3)	1 (1/16)
Mean ± SD	1.0 ± 1.00	17.33 ± 4.93	2.3 ± 0.57	1.0 ± 0.00

maximum lesion stiffness ($P < .0001$), with larger masses being stiffer than smaller masses for most histopathologic entities as assessed by shear wave elastography. Recent studies regarding the stiffness of fibroadenoma revealed a statistically significant correlation between the lesion size on US and stiffness.[25] Several reports suggested that the combined use of elastography and US is effective for distinguishing a benign breast mass from malignancy, with sensitivity of 78.0% to 100% and specificity of 21.0% to 98.5%,[15,21] increasing the accuracy of the diagnostic performance by increasing specificity and reducing the number of unnecessary biopsies, especially in small breast lesions of less than 2 cm in diameter.[19,22,23,26]

Color Doppler imaging is a valuable adjunct to US for differentiating between benign and malignant breast masses; however, the technique has a wide range of sensitivity (68.0%–91.2%) and specificity (92.7%–95%) depending on the diagnostic criteria, such as the distribution of the vascular signal around the mass or the amount of color signal in the mass.[10,12,27] However, researchers also noted that among benign breast lesions, fibroadenoma shows an increased vascular flow signal and a penetrating vascular pattern similar to malignancy, especially in cases with a large size or rapid growth.[18,27] In this study, the diagnostic accuracy was reduced in the set of US combined with color Doppler imaging compared with US alone. This finding can be explained by the relatively hypervascular feature of fibroadenoma compared with other benign breast masses.

In our results, the diagnostic performance of US increased when the radiologists considered the findings of both elastography and color Doppler imaging compared with US alone. However, the added value of color Doppler alone was not as great as that of elastography in this study. In addition, in some cases, color Doppler finding can be confusing for radiologists when distinguishing fibroadenoma from triple-negative breast cancer, resulting in a false-positive interpretation of fibroadenoma and leading to biopsy (Figure 1). Furthermore, the interobserver agreement for color Doppler score (ICC, 0.864) was reduced compared with the elastographic score (ICC, 0.948) and the interobserver agreement for the BI-RADS category assessment with elastography (ICC, 0.942) was higher than that for color Doppler imaging (ICC, 0.837). A pattern of 1 or 2 small dots of color signal on a color Doppler image can be evaluated as an avascular category or intralesional category on a case-by-case and reader-by-reader basis because of the lack of details in the BI-RADS lexicon.

In this study, we expected that by adding the elastography and color Doppler imaging to US, we could detect small triple-negative breast cancer more accurately without false-negative results and reduce benign biopsies without false-positive results. According to the results, benign biopsies could have been avoided dramatically based for a mean of 18.3 cases with 1.0 false positive result. We detected an additional 2.3 triple-negative breast cancers with the combination elastography and color Doppler imaging with US (Figure 2). However, we also missed a mean 2.0 cancers that were downgraded because of negative findings on both elastography and color Doppler imaging. All missed triple-negative breast cancer lesions were 6 to 8 mm, and both elastography and color Doppler imaging revealed negative results (Figure 3). There should be more research regarding the finding and added value of elastography and color Doppler imaging in breast lesions smaller than 10 mm.

This study had several limitations. First, we performed a retrospective analysis and included only fibroadenoma cases for the benign histologic group. Histologically, many oval or round masses that simulate triple-negative breast cancer are not fibroadenomas but types of benign fibrocystic changes or benign proliferative disorders.[28,29] Second, we did not analyze the strain and shear wave data separately. However, previous studies with intraindividual comparisons between those elastographic methods systems showed similar diagnostic performance between strain and shear wave elastography.[28,30] Third, we did not consider biopsy-related internal hemorrhage, which could alter the results of elastography or color Doppler imaging. Hemorrhage might increase the stiffness due to increased internal pressure in the mass. Last, we only performed a qualitative analysis using the BI-RADS lexicon for elastography and color Doppler imaging. If we had performed a quantitative analysis, such as shear wave elastography or a computer-assisted quantitative analysis for color Doppler US, the results might have varied. In addition, a computer-aided diagnostic system based on texture features can also be applied for distinguishing triple-negative breast cancer and benign fibroadenomas on US.[31]

In conclusion, elastography is more useful than color Doppler US for distinguishing small oval or round triple-negative breast cancer from fibroadenoma on breast US, and the combined use of elastography and color Doppler imaging with US can increase diagnostic performance, showing excellent diagnostic value for avoiding biopsy of benign masses. Further prospective studies are needed to determine how to best combine elastography and color Doppler imaging with breast US for the management of breast masses of various histologic types.

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